I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: August 2, 2007 Signature: (William K. Merkel)

AFTER FINAL AMENDMENT
EXPEDITED PROCEDURE
ART UNIT 1646

Docket No.: 9189
(01017/40451B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Brockhaus et al.

Application No.: 08/444,790 Art Unit: 1646

Filed: May 19, 1995 Examiner: Z. Howard

For: HUMAN TNF RECEPTOR

AMENDMENT UNDER 37 CFR § 1.116 AND REQUEST FOR RECONSIDERATION

Box AF
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P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is filed in response to the final Office Action mailed February 23, 2007 (the "Action"), in which all pending claims 62, 102, 103, 105-107, 110, 113, 114, 119, 123-137 and 139-144 were rejected under 35 U.S.C. §§ 103 and 112, first paragraph. Reconsideration and withdrawal of the rejections are respectfully requested in light of the following amendments and remarks. This response is timely filed with a petition for a three month extension of time.

AMENDMENTS TO THE SEQUENCE LISTING

Please replace the substitute sequence listing submitted on January 12, 2007 (12 sheets) with the substitute sequence listing (12 sheets) submitted herewith.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the applications:

Listing of Claims:

1-61 (canceled)

62. (currently amended) A protein comprising

(a) the extracellular region ~~a human tumor necrosis factor (TNF) binding soluble fragment~~ of an insoluble human tumor necrosis factor (TNF) receptor, wherein the insoluble human TNF receptor (i) specifically binds human TNF, (ii) has an apparent molecular weight of about 75 kilodaltons on a non-reducing SDS-polyacrylamide gel, ~~and~~ (iii) comprises the amino acid sequence LPAQVAFXPYAPEPGSTC (SEQ ID NO: 10), and (iv) is encoded by a nucleotide sequence obtainable from a cDNA library made from HL60 cell extracts; and

(b) all of the domains of the constant region of a human immunoglobulin IgG1 heavy chain other than the first domain of said constant region;

wherein said protein specifically binds human TNF.

63-101. (canceled)

102. (previously presented) The protein of claim 62, wherein the soluble fragment comprises the peptides LCAP (SEQ ID NO:12) and VFCT (SEQ ID NO:8).

103-124. (canceled)

125. (currently amended) The protein of claim 62 ~~106~~, wherein the protein is purified.

126. (previously presented) The protein of claim 62 ~~106~~, wherein the protein is produced by CHO cells.

127. (currently amended) The protein of claim 62 ~~106~~, wherein the protein consists of (a) ~~the soluble fragment~~ the extracellular region of the insoluble human TNF receptor and (b) all of the domains of the constant region of the human IgG1 heavy chain other than the first domain of the constant region.

128-131. (canceled)

132. (currently amended) The protein of claim [[107]] 62, 126, or 127, wherein said domains of the constant region of the human immunoglobulin heavy chain consist essentially of the immunoglobulin amino acid sequence encoded by pCD4Hγ1 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5314) ~~or by pCD4-Hγ3 vector (deposited at Deutschen Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) in Braunschweig, FRG under No. DSM 5523~~).

133-136. (canceled)

137. (currently amended) A pharmaceutical composition comprising the recombinant protein of claim [[105]] 62, 125, 126 or 127 and a pharmaceutically acceptable carrier material.

138. (canceled)

139. (previously presented) A method of binding human TNF *in vivo* comprising the step of administering to a subject the pharmaceutical composition of claim 137.

140. (currently amended) A protein comprising

(a) the extracellular region ~~a human tumor necrosis factor (TNF) binding soluble fragment~~ of the human p75 TNF receptor amino acid sequence encoded by the cDNA

insert of the plasmid deposited with the ATCC on October 17, 2006 under accession number PTA 7942; and

(b) all of the domains of the constant region of a human immunoglobulin IgG1 heavy chain other than the first domain of said constant region;

wherein said protein specifically binds human TNF.

141. (currently amended) The protein of claim 140 consisting of (a) the ~~soluble fragment~~ extracellular region of said amino acid sequence, and (b) all the domains of the constant region of the human immunoglobulin IgG1 heavy chain other than the first domain of said constant region.

142. (currently amended) The protein of claim 140

wherein the protein is expressed by a CHO ~~mammalian host~~ cell.

143-144. (canceled)

REMARKS

I. Preliminary Remarks

Applicants thank Examiners Howard and Kemmerer for the courtesy of several telephone conversations from May 23, 2007 to June 6, 2007 discussing procedural matters relating to after-final amendments.

At page 2 of the Action, the Examiner stated that the amended priority statement was allowed pursuant to 37 C.F.R. § 1.55; however, the Examiner required compliance with the requirements set out in 35 U.S.C. § 119(b) and 37 C.F.R. § 1.63(c) to perfect the claim to priority. Pursuant to 35 U.S.C. § 119(b), submitted herewith is a certified copy of European Patent Application No. 90116707.2. In addition, pursuant to 37 C.F.R. § 1.63(c), submitted herewith is a substitute Application Data Sheet, which reflects the amendment to the priority claim.

Also submitted herewith is a substitute sequence listing which corrects a typographical error in the amino acid sequence set out as SEQ ID NO: 5, a sequence which is not referenced anywhere in the present claims. The amino acid at position 24 should be a GLN (Q) rather than a GLU (E) as shown in sequence IA at page 7, lines 27-29 of the specification. The correct sequence is set out in the specification and therefore the substitute sequence listing does not add new matter to the application.

II. The Outstanding Objections and Rejections

Applicants continue to disagree with the Examiner's position that the claims are not adequately described by the specification and that the claims are obvious over Dembic *et al.* (*Cytokine* 2: 231-237, 1990) in view of Capon (US Patent No. 5,116,964). In addition, Applicants believe that the amendment to the specification to include the deposit information (at page 10, line 11) should be entered because this amendment is not new matter. Consequently, Applicants disagree with the rejection of claims 140-144, which recite such deposit information, as containing new matter and lacking enablement. Applicants intend to preserve all issues for appeal.

III. Submission of Lyman Declaration

Applicants submit herewith a Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph.D. (denoted herein as the "Declaration") in order to respond to a new position with regard to the written description rejection raised by the Examiner in this Action.

Entry of the Declaration is requested under 37 C.F.R. §1.116 because this paper is the first opportunity for the Applicants to respond to the Examiner's interpretation of the specification, including the specification's citation of Smith 1990 at page 10. The Declaration could not have been presented earlier since the position was raised for the first time in this Action. When the Patent Office advances a position or rationale new to the proceedings, an applicant must be afforded an opportunity to respond to that position or rationale by submission of contradicting evidence. See, e.g., *In re Eynde*, 480 F.2d 1364, 178 U.S.P.Q. (BNA) 470 (C.C.P.A. 1973).

The February 23, 2007 Action reiterates at pages 6-8 the Examiner's previous position, *i.e.*, that the specification only discloses a sequence missing 48 N-terminal amino acids of the 75 kD TNFR, but also newly states at pages 8-9, "While the sequence of the entire extracellular domain of the 75kD TNF receptor was publicly available in the references of Smith (1990) and Dembic (1990) at the time of filing of the instant application, there is no description in the instant specification of these specific full-length sequences, or any description that suggests using these full-length sequences in the claimed fusion proteins." The Action also states, "While the specification cites Smith (1990) on page 10, the specification does not contemplate use of the sequence of the full length extracellular domain of the receptor taught in Smith." Similarly, on page 10, the Action states, "there is no teaching in the instant specification indicating that the sequences disclosed in Dembic are relevant to the proteins of the instant invention."

In response to the newly stated interpretation of the specification and newly stated position on the relevance of published information, submitted herewith is a Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph.D. (denoted herein as the "Declaration"). Dr. Lyman is experienced in the molecular biology of Type I transmembrane receptors and is

qualified to attest to what one of skilled in the art would have understood from reading the application as of September 10, 1990. Applicants respectfully request entry of the attached Declaration to provide evidence concerning knowledge in the art and the relevance of published information to those of skill in the art.

In addition, because Applicants have sought priority benefit of European Patent Application No. 90116707.2, Applicants submit herewith a corresponding "Second Declaration of Stewart Lyman, Ph.D. Under 37 C.F.R. § 1.132" in which he states that his factual statements and conclusions with respect to the instant application apply also to the priority application as of its priority date, and that the relevant written description of both is the same.

IV. Requested Entry of Amendments

While Applicants continue to believe that the claims of the original scope are patentable, in view of the protracted pendency of this case, Applicants respectfully request entry of the proposed amendments pursuant to 37 C.F.R. §1.116(b)(2) to place the claims in better condition for allowance or to narrow issues for appeal and present claims in better form for appeal. In keeping with these goals, the number of claims has been reduced from thirty four to only eleven in the amended claim set. If an alternative amendment of the claims would expedite resolution of the case, the Examiner is earnestly requested to contact the undersigned for further discussions.

Written descriptive support for the proposed amendments is found throughout the specification. Page 35, lines 22-36 specifically discloses cDNA obtainable from an HL-60 cDNA library. The "extracellular part" and "extracellular region" of a TNF binding protein are disclosed in the examples, *e.g.*, at page 37, lines 15-18 ("extracellular part"), page 42, lines 5-7 ("extracellular region"), which use the 55 kD TNF binding protein as the exemplary TNF binding protein. The Applicants disclose, at almost every instance, that the exemplary embodiments relate to both of the 55 kD and 75 kD TNF binding proteins that are the subject of the application. See, e.g., page 9, line 19 through page 10, line 10 and page 14, lines 32-36. The use of the phrases "extracellular part" and "extracellular region" are thus

equally applicable to either the 55 kD or the 75 kD TNF receptor. In fact, Applicants specifically state that the examples are illustrative and that these examples should not limit the scope of the invention. See page 20, lines 27-30. Moreover, the application explicitly contemplates the use of soluble, TNF-binding fragments of already-known sequences, as well as those disclosed in the application: "On the basis of the thus-determined sequences and of the already known sequences which code for certain receptors, those partial sequences which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods." Page 14, lines 32-36. Accordingly, the ordinarily skilled artisan in the field is fully notified by the specification, as filed, that embodiments of the invention include the extracellular region of the 75 kD human TNF receptor.

As supplemental support, see the accompanying Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph.D., particularly paragraphs 10-17 and 24. Dr. Lyman's conclusion upon reviewing the specification, including these cited portions, is that "one skilled in the art at the time would have understood that the application contemplated that the entire extracellular region of p75 TNFR was a specific example of a soluble fragment of a TNF binding protein." Paragraph 24 of the Declaration. Thus, the proposed amendment is fully supported by the application.

Applicants respectfully request entry of the attached claim amendment under 37 CFR § 1.116 because the claim amendment puts the claims in better form for appeal and narrows the issues for appeal. The amendment of the claims to recite the extracellular region of the p75 human TNF receptor encoded by a nucleic acid obtainable from an HL60 cDNA library fully addresses and moots the rejection based on asserted lack of written description to support the breadth of the claims. Thus, the proposed amendment may properly be entered pursuant to 37 C.F.R. §1.116(b)(2) because it puts the claims in better form for appeal, and Applicants respectfully request entry of the amended claims.

Entry of the proposed amendment is also requested pursuant to 37 C.F.R. §1.116(b)(3) because it responds to new issues raised in the Action, which Applicants had not previously had the opportunity to respond to. For example, on page 13 the Action states, "the term 'insoluble human TNF receptor' does not limit the receptor to any particular naturally

occurring human receptor, but includes allelic variants as well as artificial receptors with one or more amino acid mutations to the sequence of the insoluble human TNF receptor." This newly raised interpretation of the term "human" was not raised in the prior office action or during the interview when applicants discussed the meaning of this term. Applicants disagree that the term "human" can be interpreted in such a manner to include artificial receptors. Nevertheless, in order to narrow issues for appeal, claim 62 has been amended in response to this newly raised issue to recite proteins containing the extracellular region of an insoluble human TNF receptor of about 75 kD, which is encoded by a nucleotide sequence obtainable from an HL-60 cDNA library. Similarly, claim 140, the only other independent claim among the amended claims, has been amended to recite proteins containing the extracellular region of the TNF receptor encoded by the nucleotide sequence contained in a particular deposited plasmid.

Another issue was newly raised in the Action. The Action states on page 10, "In absence of a description of the full-length extracellular domain of the 75 kD receptor for use in Applicants' claimed invention, Applicants did not have possession of the claimed invention at the time of filing." In order for Applicants to respond to this newly raised issue, Dr. Stewart Lyman was asked to evaluate what one skilled in the art at the time would have understood, from reading the specification. As part of this evaluation, he came to the factual conclusion that one skilled in the art would have understood that Applicants contemplated fusion of the extracellular domain of the p75 TNFR to all the domains of a human immunoglobulin constant region, other than the first domain. Applicants have therefore amended the claims in view of the insights gained from Dr. Lyman's declaration. Thus, there are good and sufficient reasons why the amendment was not presented earlier. Therefore, the amendment may properly be entered pursuant to 37 C.F.R. §1.116(b)(3), and Applicants respectfully request entry of the amendment.

V. Submission of Second Budapest Declaration and additional references

In response to the newly stated rejection (at page 20 of the Action) of claims 140-144 under 35 U.S.C. §112, first paragraph (enablement) because of the lack of an affidavit regarding the Budapest Treaty, Applicants submit herewith a second Budapest

Declaration and request entry of such declaration pursuant to 37 C.F.R. §1.116 to narrow the issues and place the case in better form for consideration on appeal.

Also submitted herewith is an additional reference (Heller *et al., Proc. Natl. Acad. Sci.,* 87: 6151-6155, 1990) showing TNF-binding activity of soluble fragments of the p75 TNFR in response to the Examiner's newly raised objection at page 13 of the Action that Smith (1990) did not provide TNF-binding data for the extracellular domain of p75 TNFR.

CONCLUSION

Applicants preserve the right to appeal all pending rejections and objections. If further discussion would expedite allowance of the claims and/or limitation of issues for appeal, the Examiner is asked to contact the undersigned at the number below.

Dated: August 2, 2007

Respectfully submitted,

By Li-Hsien Rin-Laures

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